








CLINICAL FEATURES
REVIEW



Potential neurological manifestations of COVID-19: a narrative review

Joseph V. Pergolizzi Jr ^a, Robert B. Raffa ^{b,c}, Giustino Varrassi ^d, Peter Magnusson ^{e,f}, Jo Ann LeQuang ^a, Antonella Paladini ^g, Robert Taylor ^a, Charles Wollmuth^a, Frank Breve^{a,h}, Maninder Chopraⁱ, Rohit Nalamasu^j and Paul J. Christothe NEMA Research Group^k

^aNEMA Research, Inc., Naples, FL, USA; ^bTemple University School of Pharmacy, Temple University, Philadelphia, PA, USA; ^cUniversity of Arizona College of Pharmacy, Tucson, AZ, USA; ^dPaolo Proccacci Foundation, Rome, Italy; ^eCentre for Research and Development, Region Gävleborg/Uppsala University, Gävle, Sweden; ^fDepartment of Medicine, Cardiology Research Unit, Karolinska Institutet, Stockholm, Sweden; ^gDepartment MESVA, University of L'Aquila, L'Aquila, Italy; ^hDepartment of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, PA, USA; ⁱDecision Alternatives, LLC, Frederick, MD, USA; ^jDepartment of Physical Medicine and Rehabilitation, University of Nebraska Medical Center, Omaha, NE, USA; ^kDivision of Pain Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

ABSTRACT

Neurological manifestations are increasingly reported in a subset of COVID-19 patients. Previous infections related to coronaviruses, namely Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS) also appeared to have neurological effects on some patients. The viruses associated with COVID-19 like that of SARS enters the body via the ACE-2 receptors in the central nervous system, which causes the body to balance an immune response against potential damage to nonrenewable cells. A few rare cases of neurological sequelae of SARS and MERS have been reported. A growing body of evidence is accumulating that COVID-19, particularly in severe cases, may have neurological consequences although respiratory symptoms nearly always develop prior to neurological ones. Patients with preexisting neurological conditions may be at elevated risk for COVID-19-associated neurological symptoms. Neurological reports in COVID-19 patients have described encephalopathy, Guillain-Barré syndrome, myopathy, neuromuscular disorders, encephalitis, cephalgia, delirium, critical illness polyneuropathy, and others. Treating neurological symptoms can pose clinical challenges as drugs that suppress immune response may be contraindicated in COVID-19 patients. It is possible that in some COVID-19 patients, neurological symptoms are being overlooked or misinterpreted. To date, neurological manifestations of COVID-19 have been described largely within the disease trajectory and the long-term effects of such manifestations remain unknown.

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Introduction

The neuroinvasive potential of the Severe Acute Respiratory Syndrome novel coronavirus, SARS-CoV-2, is being recognized, with enhanced awareness that the associated infection, Coronavirus Diseases 2019 (COVID-19), might result in neurological injury. Indeed, there is a growing body of evidence to suggest that a subset of COVID-19 patients will experience neurological manifestations of the infection [1]. Since genomic studies show that the SARS-CoV-2 virus has similar homological sequences with two of its beta-coronavirus predecessors, the SARS-CoV associated with Severe Acute Respiratory Syndrome (SARS) [2] and the virus associated with Middle Eastern Respiratory Syndrome (MERS) [3], it is helpful to review the neurological symptoms of these two earlier diseases as the plausible link between COVID-19 and neurological symptoms are explored. Furthermore, the pathophysiological pathways of these three conditions (COVID-19, SARS, and MERS) might be expected to be similar [4–6]. Neurotropism has been observed in both MERS and SARS [7–9], and there are early findings of certain neurological manifestations in COVID-19 patients [4,10]. The RNA of the SARS-CoV-2 virus has been

identified in the cerebrospinal fluid of a COVID-19 patient, demonstrating its neurotropic potential. It is clinically relevant to determine how the SARS-CoV-2 virus can access the central nervous system (CNS) and whether the neuronal injury caused by the virus might be connected to the injury of the autonomic nervous system.

The transmission of a novel infectious pathogen among humans such as the SARS-CoV-2 may be complicated, but it is far from rare. As many as 75% of emerging human infections have some connection to a zoonotic disease [11]. Typically, viral, bacterial, fungal, or parasitical pathogens may emerge due to one or a combination of factors: human and animal interaction, changes in human or animal behavior, consumption of exotic animal foods, globalization, world travel, or things that disrupt human and animal interactions, such as wars, natural disasters, and environmental changes. The pathogen itself may play a role in its pattern of emergence by mutation; in some instances, humans may facilitate the rapid progress of these mutations by the use of antimicrobials. Thus, while often multifactorial and complex, the sudden emergence of a novel infectious agent is

not a novelty [12]. The novel SARS-CoV-2 virus, which first appeared in 2019, is just one of several coronaviruses that have caused epidemics in the past two decades. These pathogens are sometimes able to adapt to new hosts, as occurred with the zoonotic SARS-CoV-2 virus, which appears to have originated in bats, then rapidly accommodated to human hosts [13].

Coronaviruses are single-stranded, positive-sense, enveloped RNA viruses in the nidovirales order that are categorized into four genera: alpha, beta, gamma, and delta. The SARS-CoV-2 virus associated with the COVID-19 epidemic is a beta-coronavirus. Seven known coronaviruses affect humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2. Many coronavirus-related illnesses are mild. In fact, coronaviruses were first studied in the 1960s as being agents of the common cold [14]. Nevertheless, of these viruses, only MERS-CoV, SARS-CoV, and SARS-CoV-2 are associated with potentially severe symptoms and fatal outcomes [15].

Once in the body, viruses may invade the CNS through hematogenous spread defined by viremia. Viruses may also enter the CNS through retrograde neuronal dissemination, which occurs when the virus infects peripheral neurons, subsequently spreading to the spine and brain by way of the existing neuronal transport mechanisms.

It is the aim of this narrative review to describe what is known about neurological manifestations of SARS, MERS, and COVID-19, with special emphasis on reports about neurological symptoms in COVID-19.

Methods

The authors searched the peer-reviewed medical literature using the PubMed database of the National Institutes of Med for COVID-19 resources searching for 'neurology,' 'neurological symptoms,' and 'neuropathy.' The bibliographies of relevant articles were searched as well. The literature on COVID-19 is vast and expanding rapidly, but many articles are short commentaries, case studies, and correspondence. The search covers materials published through 17 August 2020.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Results

Far more is known and reported on neurological complications with SARS and MERS than for COVID-19 although the nature of the pandemic and the clinicians reporting from the front lines is rapidly generating a large body of literature. In a systematic review that identified COVID-19 cases with neurological complications ($n = 82$), the mean age of the patient was 62.3 years, 37.8% were female, and 48.8% developed cerebrovascular insults, 28% neuromuscular disorders, and 23% encephalitis or encephalopathy [16].

Viral entry and potential neurological consequences

The viruses associated with both SARS and COVID-19 enter the brain via a process involving the angiotensin-converting enzyme (ACE)-2 receptors located in the CNS [17–19], unlike the MERS virus, which gains entry via the plasma membrane or in the endosomes [20]. ACE-2 receptors are expressed in many parts of the body and are particularly densely expressed in the nasal mucosa. Coronaviruses that enter the body via the nasal mucosa may disrupt the nasal endothelium, cross the epithelial barrier, and then directly enter the lymphatic or circulatory system, accessing the CNS [21]. The SARS-CoV has been detected in the brain, and it is thought entry occurred by way of the olfactory nerve. Since there have been studies that located the SARS-CoV virus in the CNS but not the lung, it suggests that there is a direct pathway from the olfactory point of entry into the CNS [22]. Alternatively, a high viral load in the brain following a pulmonary infection might mean the virus entered the brain from the respiratory system; e.g., the vagus nerve links the respiratory system to the nucleus ambiguus and solitary tract nuclei of the brainstem. It has been speculated that the cardiorespiratory center of the brain may be involved in the severe acute respiratory distress in some patients with COVID-19 [23]. The more common form of respiratory failure in COVID-19 patients is Type 1 (gas exchange dysfunction resulting in hypoxia and low levels of carbon dioxide), which is more likely to be associated with pneumonia than brain dysfunction [24]. Type 2 respiratory failure, which involves both hypoxia and high levels of carbon dioxide due to ventilatory failure would be more suggestive of neurological dysfunction, and this occurs less frequently in COVID-19 patients [25].

Any viral invader of the CNS creates stress within the body, because the host must balance its natural immune response to destroy the pathogen while, at the same time, minimizing damage to nearby nonrenewable cells [26]. Once in the CNS, viruses that affect neurons are far more dangerous than viruses that target the leptomeninges, which can restore themselves. The CNS has a highly nuanced system of responses to viruses, which can cause considerable harm to the body should it become uncontrolled.

Coronaviruses such as the SARS-CoV-2 can enter the body via the nasal mucosa and may disrupt the nasal endothelium, cross the epithelial barrier, and then enter the CNS via the lymphatic or circulatory system [21]. The blood-brain barrier has a pore size of about 1 nm and coronaviruses are substantially larger [9], and this likely protects the brain from coronavirus invasion in many individuals. However, neuroinvasive viruses can cross the blood-brain barrier by brain viremia, inflammatory processes (making microvascular endothelial cells vulnerable), or infecting leukocytes that then cross the blood-brain barrier in the manner of a Trojan horse [27]. The entry of the virus via the olfactory endothelium with transit of the virus across the cribriform plate would allow the virus to enter the brain by circumventing the blood-brain barrier entirely [27].

In theory at least, the coronavirus could invade the CNS using a passive mechanism such as hematogenous spread; in this case, the virus goes dormant and is carried toward the

CNS, only to re-activate at some point to infect endothelial cells of the blood-brain barrier or infect leukocytes that then act as the reservoir for further viral dissemination [28]. The neurological symptoms associated with the H1N1 influenza virus had earlier been explained by an autoimmunity model [29]. The autoimmunity model of coronavirus infection of the CNS, likewise unproven, maintains that neural tissues and blood vessels perceive both viral and myelin antigens as the same because of autoreactive T-cells. Autoimmunity would be limited to patients who were genetically predisposed [29].

The SARS-CoV-2 associated with COVID-19 belongs to the same clade of beta-coronaviruses as the MERS-CoV and the SARS-CoV viruses, although its homological sequence more closely resembles SARS-CoV than MERS-CoV [2]. The respiratory symptoms that occur in genetically related beta-coronaviruses, such as MERS-CoV and SARS-CoV are similar, two infections with which the global healthcare community has had years of clinical experience [30]. While it cannot be stated unequivocally that the neurological symptoms of these viral infections will be the same, it forms a good starting point.

Middle eastern respiratory syndrome

MERS was first identified in September 2012 in a 60-year-old man in Jeddah, Saudi Arabia, who presented with pneumonia complicated by renal failure [31]. Sporadic cases were reported outside of the Middle East up until 2015, when an outbreak in South Korea occurred with 186 confirmed infections and 38 deaths [32]. MERS has established associations with encephalomyelitis, vasculitis, Guillain-Barré syndrome (GBS), and encephalitis of the brain stem [21].

The clinical course of MERS ranges from asymptomatic cases (about 4%) to severe pneumonia with multiorgan involvement and negative patient outcomes [15]. While pulmonary, gastrointestinal, renal, and hematological complications have been reported in MERS patients, there are fewer reports of neurological complications [15]. In fact, the MERS-CoV virus has never been isolated from neural tissue in human beings [28].

In a study of 737 hospitalized MERS patients in South Korea, the most commonly reported symptoms were respiratory symptoms (13.6%), fever (11.1%), fatigue (11.1%), myalgia (9.2%), and gastrointestinal symptoms (7.5%) [32]. In a study of 23 MERS patients from South Korea, 17.4% experienced neurological symptoms either during or following MERS treatment [33]. These neurological complications occurred about two to three weeks after the onset of respiratory symptoms [33]. A study from Saudi Arabia (n = 70) reported that 24.7% of MERS patients experienced confusion and 8.6% had a seizure [34]. In this study, fever was present in 61.4% of patients, dyspnea occurred in 60%, an 54.3% had a cough. MERS symptoms were typically severe with 70% of those hospitalized in this study requiring intensive care and 60% of this cohort died [34].

The literature reports a fatal case of a 34-year-old woman with diabetes hospitalized for MERS, who two weeks after diagnosis developed a headache with nausea and vomiting [15]. An urgent computed tomography scan showed right frontal lobe intracerebral hemorrhage with massive brain

edema; laboratory findings showed disseminated intravascular coagulation, including thrombocytopenia and a prolonged coagulation profile. In another case, a 28-year-old man was hospitalized in the intensive care unit for MERS complicated by bacterial pneumonia and had to be put on a ventilator for respiratory distress. Unfortunately, after initial improvement, he reported weakness and tingling in his legs that made it impossible for him to walk. Using neuroimaging scans, cerebrospinal fluid analysis, nerve conduction velocity studies, and spinal imaging, a diagnosis was made of critical-illness polyneuropathy. He was treated with intravenous (IV) immunoglobulin 400 mg/kg daily for five days and was discharged in 40 days; gradual improvement was noted over the next 6 months [15].

Severe acute respiratory syndrome

SARS broke out in Hong Kong, Taiwan, Canada, and other locations in 2003. It has been reported to be associated with encephalitis, ischemic stroke, and polyneuropathy [35]. Seizures have been mentioned as the first symptom of SARS-related encephalitis [36]. In a necropsy study of eight patients who died of SARS, there was evidence of SARS-CoV infection in the brain cortex and hypothalamus [37]. Particles from the SARS-CoV virus have been found in the brains of patients infected with SARS, most frequently in brain neurons [37–39]. Murine studies found that intranasal injections of both MERS-CoV and SARS-CoV could enter the brain, presumably via the olfactory nerves [40,41]. Among the areas of the brain infected, the brain stem was a primary, but not exclusive, target for both MERS-CoV [41] and SARS-CoV [40,42].

Neurological sequelae of SARS have been only sporadically reported. Acute olfactory neuropathy has been reported in a case study of a 27-year-old female SARS patient who was diagnosed with SARS in 2003, hospitalized, and recovered with combination therapy of antiviral therapy (ribavarin plus steroids) [43]. Fever persisted for about three weeks from onset of symptoms. She was discharged from the hospital at around the same time she reported the paroxysmal bilateral loss of her sense of smell. An otolaryngologic examination, biochemistry tests, and subsequent magnetic resonance imaging scans showed nothing unusual with no lesions that might account for her loss of olfaction. Now 2 years after her recovery from SARS, she still has not regained her sense of smell [43]. The common causes of anosmia include structural defects in the nasal cavity or sinuses, head injury, brain trauma, brain lesions, or drug-induced loss of olfaction, and in her case, these could all be ruled out. It was postulated that her anosmia was a coronavirus-induced form of olfactory neuropathy [43].

Neuromuscular symptoms associated with SARS have also been reported. A 51-year-old woman in Taiwan developed probable SARS shortly after her husband was diagnosed [44]. She was hospitalized and intubated and had no evidence of respiratory syncytial virus; however, a bone-marrow biopsy showed evidence of infection-related hemophagocytic syndrome. Her condition gradually improved and she was extubated, but she complained of weakness, numbness, and paresthesia in her legs. Ten days after extubation, a neurological examination showed good mental clarity with

intact cranial nerves, but symmetric loss of muscle strength in her legs and mild weakness in the hands. These conditions improved slowly and two months later, a neurological examination reported only mild loss of leg strength and slight numbness in the toes of her right foot [44].

A case report from Hong Kong describes a 59-year-old woman with severe SARS who developed status epilepticus; evidence of the virus was found in her cerebrospinal fluid [45]. Another case report describes a pregnant patient with SARS who experienced a generalized convulsion with suspected nervous system invasion by the virus [46].

The neurological manifestations observed in SARS include peripheral axonal neuropathy and elevated muscle enzymes, which might be caused by extensive virus-driven vasculitis [38,47]. These were considered to be polyneuropathic and/or myopathic symptoms associated with critical illness [47].

COVID-19

Neurological symptoms have been sporadically reported in COVID-19 patients but have not yet been well studied [48,49]. The current body of evidence suggests that the SARS-CoV-2 can affect the nervous system in previously unsuspected ways [50]. The neuroinvasive capabilities of the SARS-CoV-2 doubtless exist but remain to be elucidated. Observed neurological symptoms of COVID-19 include febrile seizures, convulsions, mental status changes, and encephalitis [51]. Among the most commonly reported possibly neurological symptoms of COVID-19 are nonspecific symptoms, such as headache, myalgia, dizziness, and fatigue [21]. In a study at a single center in China ($n = 214$), 36.4% ($n = 78$) of hospitalized COVID-19 patients had what were identified as neurological symptoms [52]. In a multicenter retrospective study from Europe of 417 patients who recovered from mild to moderate COVID-19, 86% reported olfactory dysfunction and 88% problems with taste. In fact, in 12% of patients, the loss of the sense of smell was the first symptom of COVID-19 [53]. The loss of smell has emerged as being more prevalent among patients infected with COVID-19 than patients infected with other viruses or with other types of respiratory conditions [54] and has been recommended as a symptom that may help guide earlier diagnosis and treatment of COVID-19 [55]. In a meta-analysis ($n = 1,627$ patients, 10 studies), a loss of the sense of smell was reported in 53% of COVID-19 patients [55].

It appears that the frequency of neurological symptoms is associated with COVID-19 disease severity. In the aforementioned study of 214 hospitalized patients with COVID-19 infection (41% severe and 59% non-severe disease), severe patients were more likely than non-severe patients to have neurologically related manifestations (45.5% vs. 30.2%, respectively). In this study, the most frequently reported neurological manifestations for severe and non-severe patients, respectively, were acute cerebrovascular disease (5.7% vs. 0.8%), impaired consciousness (14.8% vs. 2.4%) and skeletal muscle injury (19.3% vs. 4.8%) [52]. This does not take into account more diffuse symptoms, such as confusion or headache, which may also be neurological [51].

Most COVID-19 patients seem to exhibit pulmonary symptoms before neurological ones [49]. About a third of

diagnosed COVID-19 patients have some form of symptomatology of suspected neurological origin, which might include headache, dizziness, impaired consciousness, ataxia, epilepsy, and cerebrovascular disease [49]. Besides an impaired or absent sense of smell or taste, vision disturbances, neuralgia, and skeletal muscle damage have also been reported [49]. Nucleic acid from the SARS-CoV-2 virus has been detected in the cerebrospinal fluid of patients, and the virus itself has been identified in brain tissue on autopsy of patients who died of COVID-19 [49]. Such findings are rare but confirm that the SARS-CoV-2 virus can enter the CNS. A 24-year-old Japanese man with COVID-19 presented with generalized epileptic seizures and decreased consciousness; RNA from the SARS-CoV-2 was not detectable in his nasopharynx but was identified in the cerebrospinal fluid [56]. Using a polymerase chain reaction (PCR) assay, the SARS-CoV-2 was likewise detected in the cerebrospinal fluid of an obese 40-year-old female COVID-19 patient with diabetes [57].

Neurotropism in COVID-19

In general, the distribution of the host's receptor cells determine viral tropisms [58–60]. Neurotropism appears to be a common feature of coronaviruses in general, as these viruses share similar viral structures and pathways [50]. Both SARS-CoV and SARS-CoV-2 enter the body via an ACE-2 receptor-facilitated manner; ACE-2 receptors are highly expressed in the epithelial structures of the airway and vessels, lung parenchyma, the kidney, and cells of the small intestine [61,62]. Unlike its predecessor, the SARS-CoV, however, the SARS-CoV-2 virus, enters human cells in a process involving dipeptidyl peptidase 4 (DPP4), which is most abundant in the lower respiratory tract, kidney, small intestine, liver, and immune system [63]. The SARS-CoV virus does not utilize the DPP4 system and is not associated with lower respiratory tract infections [4].

The expression of ACE-2 receptor cells and DPP4 are very low in the CNS [64], and the route by which coronaviruses enter the CNS is subject to speculation. It has been suggested that they invade peripheral nerve terminals first, and, in that way, enter onto a synapse-connected pathway into the CNS [23,65–67]. This so-called 'trans-synaptic transfer' has been observed for other lesser-known coronaviruses, such as HEV67N and the avian bronchitis virus [10,23,65,67,68]. Indeed, the HEV67N virus has been demonstrated in porcine studies to invade the brain; first, it infects the nasal mucosa, lungs, and small intestines and then peripheral nerves transport it retrogradely to the medullary neurons [66]. The avian bronchitis virus infects the brainstem of mice and may cause neuroanatomical disruptions. The mice that died of respiratory failure may have had failure of the cardiorespiratory center within the brain stem [23,64,69].

COVID-19 and specific neurological conditions

Neurological manifestations of COVID-19 may be mild and diffuse, such as headache and myalgia or severe, such as intracranial infections [50]. While severe neurological symptoms have been reported and are associated with worse outcomes, they appear to be rare [50]. It is important in this

connection to note that COVID-19 may cause specific neurological symptoms, exacerbate preexisting neurological conditions, or unmask preexisting neurological conditions that had not yet been diagnosed. Any number of infections can unmask an undiagnosed neurological condition, resulting in their overt emergence or exacerbation. Thus, a portion of COVID-associated neurological and neuromuscular symptoms may be unmasked in the pandemic rather than directly caused by the SARS-CoV-2 virus [70]. In a study from the United Kingdom of 43 patients with a confirmed COVID-19 diagnosis or where the diagnosis of COVID-19 was deemed 'probable' or 'possible' based on World Health Organization criteria, 10/43 patients had encephalopathy with delirium/psychosis and no abnormalities on magnetic resonance imaging or in cerebrospinal fluid, 12/43 exhibited inflammatory syndromes of the central nervous system, including encephalitis, 8/43 had ischemic stroke, 8/43 had peripheral neurological disorders (predominantly Guillain-Barré syndrome), and 5/43 with miscellaneous central disorders [71]. These neurological disorders were similar to those associated with other coronavirus epidemics.

An online network of rapid-response case report notifications in the United Kingdom was launched in April and collected 23 days of data in April 2020 about COVID-19 patients with neurological symptoms. A total of 153 cases were reported that met clinical definitions. The median patient age was 71 years (range 23–94, interquartile range 58–79) with 62% presenting with a cerebrovascular event, 74% with ischemic stroke, 12% with intracerebral hemorrhage, and 1% with central nervous system vasculitis [72]. In the ALBACOVID registry study of 841 hospitalized COVID-19 patients in Spain evaluated in March 2020, 57% had some neurological symptom(s), with myalgia, headache, and dizziness more likely to occur early in the diseases; neurological complication were the main cause of death in 4% of the decedents in this study population [73].

Patients with confirmed or suspected COVID-19 may have preexisting neurological conditions or be at elevated risk for them, for example, patients with atrial fibrillation are at risk for stroke. Certain motor neuron diseases, such as amyotrophic lateral sclerosis, may put patients at elevated risk for infection in general. Of particular concern are patients with muscular dystrophies associated with weakness of ventilator muscles or cardiomyopathy who are exposed to COVID-19. In such cases, patients may recover from COVID-19 but not go back to their baseline neuromuscular functioning [70].

Encephalopathy

Encephalopathy, which often presents in infectious disease patients as delirium, is a brain disorder that causes acute or subacute dysfunction in terms of consciousness or altered mental states. The elderly, people with cognitive deficits, and people with hypertension are elevated risk for developing an altered mental state with COVID-19 [52,74]. Cerebral edema, a dangerous condition which can cause elevated intracranial pressure and encephalopathy, has been identified in COVID-19 decedents [75]. Those with a history of neurological damage and acute respiratory distress are at elevated risk for

developing encephalopathy as the initial COVID-19 symptom [76]. The risk becomes greater as the COVID-19 becomes more severe; altered consciousness occurs in 2.4% of mild and 15% of severe COVID-19 patients [52]. The risk for delirium, like the risk for worse outcomes with COVID-19, is also associated with older age [77]. The use of sedatives, which is common in critically ill patients, may also be associated with the risk for delirium [78,79]. Social distancing mandated for COVID-19 may actually contribute to the rate of delirium of certain COVID-19 patients, who may feel desperate and panicked as they are isolated, separated from family, alone, and/or denied religious support from a clergyperson [77].

Delirium in hospitalized COVID-19 patients may be the result of direct CNS invasion, induction of CNS inflammatory mediators, a secondary effect of other organ system failures, the effect of sedation, the result of prolonged mechanical ventilation, a psychological manifestation, or caused by environmental factors [77]. In cases of COVID-19, it is thought that delirium caused by direct invasion of the virus into the CNS is relatively rare, but possible, and would likely be accompanied by seizures, altered states of consciousness, or signs of increased intracranial pressure [39,46].

The rates and presentation of encephalopathy and delirium in COVID-19 patients has not been studied. Delirium in COVID-19 patients may be under-reported to date, indeed delirium is thought to be widely under-reported for various conditions unless it is being specifically monitored [79–82]. Case studies of COVID-19-associated delirium appear in the literature [83,84]. Acute necrotizing encephalopathy, although relatively rare, has also been diagnosed in a hospitalized COVID-19 patient [85]. Overall, ICU patients on mechanical ventilation have rates of delirium as high as 70% to 75%, and delirium is associated with mortality and long-term cognitive impairment [86–88].

The causes of COVID-19-associated encephalopathy may involve multiple factors, including metabolic causes, hypoxia, and drug therapy. Symptomatic treatment involves antipyretics, anticonvulsants, and treatment for hypoxia [21]. Early signs of delirium in COVID-19 patients might suggest CNS involvement and, as such, might indicate heightened risk for impending respiratory failure [77].

In a study of 27 pediatric COVID-19 patients with multi-system inflammatory syndrome, 15% (n = 4) exhibited new-onset neurological symptoms, such as encephalopathy, headaches, brainstem, and cerebellar signs, weak muscles, and poor reflexes [89]. Cerebrospinal fluid testing in two patients were acellular; three patients underwent nerve conduction and electromyographical studies, which revealed mild myopathic and neuropathic deficits. All four patients improved, two of whom made a complete recovery over the course of the study [89].

Guillain-Barré syndrome (GBS)

GBS typically involves demyelination and presents in both upper and lower limbs. While there is no clear evidence to date associating the SARS-CoV-2 virus with GBS, other viral infections, such as influenza and the Epstein-Barr virus, have

been linked to GBS. The association is based on the idea that there can be molecular mimicry between certain viral proteins and the gangliosides and other proteins on the peripheral nerves. This can result in an ‘innocent bystander attack’ against the myelin sheath or axon of the peripheral nerve [70]. GBS is a complex disorder and has been recognized as a para-infectious neurological disease, and has associations with the Zika virus that were documented during the 2015–2016 Zika epidemic [90].

It is not known if the coronavirus can damage peripheral nerves [44]. The literature reports on several cases that suggest a link between COVID-19 and GBS [91–94], for example, the case of a 62-year-old COVID patient with GBS; however it is unclear if this patient, who had comorbid lymphopenia and thrombocytopenia, developed GBS and COVID-19 independently but concurrently, or if COVID-19 might have caused the GBS [95]. It must likewise be considered that COVID-19-associated neurological manifestations may emerge after the initial infection. Thus, while there is currently no evidence that COVID-19 can cause GBS, it is an area worthy of further investigation.

It should be noted in this context that clinicians may sometimes observe peripheral neuropathies, for example based around the ulna, that have to do with prolonged intubation periods in a position that impinges the cubital canal.

Myopathy and neuromuscular disorders

Myalgia and fatigue are common symptoms of COVID-19 and a study of COVID-19 patients found 44% to 70% of hospitalized patients had these symptoms and 33% had increased creatine kinase (CK) [10,96]. However, the nature of the rapid outbreak and spread of the virus did not allow for thorough workup of such COVID-19 patients that might have included electromyography testing, muscle imaging, or histopathological examinations. Myalgia occurred in about a third of SARS patients [97], and rhabdomyolysis has been observed as well [47,98].

Encephalitis

Encephalitis or inflammation of the brain may be caused by a viral infection. The symptoms of encephalitis include fever, headache, seizures, altered consciousness, and behavioral disorders. A case report from China describes encephalitis in a male patient with COVID-19 with no traces of the SARS-CoV-2 in his cerebrospinal fluid. His main symptom was altered consciousness but the condition was self-limiting and the patient recovered from both COVID-19 and encephalitis [99]. Although unusual, patients with COVID-19 may present with encephalitis rather than the typical respiratory symptoms [57].

COVID-19 patients with encephalitis may also experience seizures. In particular, it is important to note that nonconvulsive status epilepticus (NCSE) may occur in such patients. The Salzburg Consensus Criteria for Nonconvulsive Status Epilepticus was published in 2015 and provides terminology definitions and identified specific EEG tracings associated with NCSE [100]. NCSE may be evident on electroencephalography (EEG), so that continuous EEG monitoring may be appropriate

for critically ill patients in general [101]. In comatose patients, NCSE has a prevalence between 5% and 48% [102]. Its prevalence specifically in COVID-19 patients is not known.

Cephalgia/headache

Early reports out of Wuhan described headache and decreased responsiveness of patients as an early indicator of potential neurologic involvement associated with the SARS-CoV-2 infection [103]. Headaches have been reported in 11% to 34% of hospitalized COVID-19 patients [104]. Among COVID-19 patients who developed symptoms, the incidence of headache is 6% to 10% and headache was often among the presenting symptoms [104]. Initial reports of the so-called ‘COVID-19 headache’ describe bilateral cephalgia characterized by pulsating pain in the temporoparietal region, forehead, or periorbital region. Such headaches were limited to active periods of the COVID-19 infection and resisted conventional analgesia [104]. While it is plausible that these headaches relate to the viral invasion, they may also be a byproduct of cytokine storm or have some other etiology [105].

Critical-illness polyneuropathy (CIP)

Acute neuropathy or CIP may develop in patients suffering a number of severe illnesses. CIP typically remits as the patient recovers from the illness [44]. Signs and symptoms of CIP include reduced compound muscle action potentials amplitude, abnormal spontaneous unilateral activities in the diaphragmatic needle electromyography evaluation, abnormal F responses, and an abnormal H reflex on electrodiagnostic studies [106]. The pathogenesis of CIP is not well elucidated and may involve a systemic inflammatory response to sepsis that damages the nerves [107]. Its prevalence among COVID-19 patients is not known.

Cerebrovascular conditions

Vascular comorbidities seem to pose a risk factor for worse outcomes with COVID-19 [108]. Stroke is emerging as an increasingly important adverse event in COVID-19 patients. From a retrospective single-center study in China ($n = 221$), risk factors for stroke in COVID-19 patients appear to be: older age, more severe COVID-19, history of hypertension, diabetes, cerebrovascular diseases, and any marked inflammatory or pro-coagulant response, such as a high C-reactive protein or D-dimer level [108]. Cerebrovascular conditions may present as neurological symptoms in COVID-19 patients [21].

Parkinson’s disease (PD) and movement disorders

The etiology of PD likely involves the interplay of genetic and environmental factors, but viruses have been implicated in causing parkinsonism and other movement disorders [109,110]. In a study using the cerebrospinal fluid of 67 patients (20 with PD, 29 without PD but with another neurological disorder, and 18 healthy controls), the PD patients had a significantly higher mean cerebrospinal fluid antibody response to two specific coronaviruses (MHV-JHM and MHV-

A59) than controls or patients with other neurological disorders. It was theorized that some strain of coronavirus might contribute over the long term to the development of PD [110]. This may relate to the epidemiological observation that people who live on farms or grow up in farming communities have a higher risk of developing PD than others, possible due to zoonotic transmission of coronaviruses [111,112].

There is no compelling evidence to suggest that patients with PD are more likely to contract COVID-19 or that they are at elevated risk for worse COVID-19 outcomes [113]. However, PD is associated with decreased respiratory function, which might contribute to respiratory distress in any number of infections, including COVID-19 [114]. Furthermore, PD is comorbid with a number of disorders, including cerebrovascular disease, heart failure, and coronary artery disease, any of which would elevate risk of worse outcomes if COVID-19 was contracted [22].

Pulmonary conditions

It has been postulated that the neuroinvasion of the brain's medulla oblongata region by the SARS-CoV-2 virus might impair cardiorespiratory control centers and, in that way, lead to respiratory distress and failure [4]. The literature reports a COVID-19 patient who lost the involuntary process of breathing and suffered respiratory failure [115]. ACE-2 receptors are expressed abundantly in the body, even in the brain, and particularly in the brain stem which controls respiration [116]. In the event that the SARS-CoV-2 virus might enter the microcirculatory system of the brain, it may access ACE-2 receptors in the capillary endothelium. In such a situation, the virus can cause damage to the endothelium itself, enter the brain, and cause neuronal destruction [116]. Better understanding is urgently needed to elucidate the role of the SARS-CoV-2 virus in the brain and to risk-stratify patients who may be suffering COVID-related brain damage.

Clinical management of neurological symptoms in COVID-19 patients

Symptoms frequently reported by COVID-19 patients, such as headache, dizziness, nausea, vomiting, confusion, and fatigue may be neurological, or they may actually be manifestations of hypoxia, respiratory distress, metabolic acidosis, or drug reactions [84]. Such generalized symptoms occur with many types of infections, can be vague and diffuse, and may be difficult for the patient to associate specifically with the COVID-19 infection. Thus, many neurological manifestations of COVID-19 are overlooked, particularly in a pandemic situation when healthcare resources are overwhelmed. For that reason, it is important to consider neurological assessments of hospitalized COVID-19 patients. Serum urea, creatinine, electrolyte, and blood gas tests may be helpful to indicate if there is CNS involvement. The loss of smell and/or taste early in the course of the disease may be significant and point toward neurological involvement [117]. Alterations to the senses of taste and smell have been reported in early-stage COVID-19 cases without complications and suggest that the virus is moving toward the olfactory bulb of the brain, which would

permit it to enter and possibly affect the brain [118]. However, it must be noted that anosmia and ageusia can also be reported in the setting of non-COVID-19 upper respiratory tract infections.

Treating neurological symptoms can be challenging as drugs that suppress the immune system may be contraindicated for COVID-19 patients. There is evidence that the use of corticosteroids may prolong viral shedding [119,120]. Symptoms for neurological problems may be addressed, with first-line strategies such as controlling body temperature, offering anticonvulsants, and treating hypoxia.²¹ Second-line treatments for neuroinflammation involve IV immunoglobulin or plasma exchange, but IV immunoglobulin may increase the risk of thromboembolism. Furthermore, there is emerging concern of the possibility of microthrombosis in COVID-19 patients [121]. Third-line strategies for neuroinflammation in COVID patients may carry higher risks, and include such pharmacological agents as cyclophosphamide and rituximab [121].

Typically, COVID-19 patients present with respiratory symptoms before neurological ones, but atypical presentations, although rare, have been reported. When neurological symptoms are present in suspected COVID-19 patients, it may be important to test and, if necessary, treat them for COVID-19 first and then address the neurological disorder afterward [49]. Although not yet fully characterized, neurological symptoms related to COVID-19 are thought to be possible following resolution of the COVID-19 infection.

In the hospital, distinct and separate areas for neurological emergencies versus COVID-related emergencies may be helpful in order to preclude that a patient with a neurological emergency but not COVID-19 does not come inadvertently in contact with a COVID-19 patient. When treating patients with neurological symptoms but no confirmed COVID-19 diagnosis, physicians, and other clinicians should ask about fever, sore throat, exposure history in the past two weeks, and so on [49]. Testing is important, particularly if there is any reason to suspect possible COVID-19 infection. COVID-19 patients who have suffered neurological complications, including stroke, may require acute rehabilitation or, in some cases, long-term residential-skilled nursing care.

Some patients who undergo prolonged hospitalization with extended periods prone in bed during mechanical ventilation may present following hospitalization with myopathy or neuropathy following acute respiratory distress syndrome, possibly necessitating extracorporeal membrane oxygenation (ECMO) therapy. Other presentations may include reversible posterior encephalopathy or the sequela of severe stroke of a large blood vessel. Weakness acquired through prolonged stays in intensive care, critical-illness polymyopathy, or polyneuropathy can occur with acute respiratory distress syndrome and may require a multidisciplinary approach for rehabilitation and recovery [122].

Discussion

As scientists and clinicians concentrate on the complexities of the SARS-CoV-2 virus and better treatment strategies for COVID-19, it is possible that neurological manifestations of COVID-19 are being overlooked or misinterpreted [117]. In

general, neurological symptoms can be under-diagnosed or even entirely overlooked as neurological manifestations, such as delirium in the critically ill COVID-19 patients or infected outpatients who do not consider a loss of the sense of smell or taste related to COVID-19. As such, clinicians on the front lines of COVID-19 care should be cognizant of possible neurological manifestations of this novel virus. Patients with suspected or diagnosed COVID-19 should be asked about the loss of smell and taste and educated that this is an important symptom to bring to the attention of the provider.

Neurological symptoms of COVID-19 have to date mainly been described within the trajectory of the infection. However, it is plausible (although far from established) that neurological sequelae from COVID-19 may emerge after the patient has recovered from the primary infection and persist for long periods after recovery. For example, it is not known if an elderly patient who recovers from a severe case of COVID-19 with cognitive dysfunction will suffer persistent cognitive deficits. The long-term burden on both caregivers and the health-care system that might be posed by COVID-19 survivors with neurological or cognitive impairment may turn out to be very important, although it is one that is rarely discussed, even hypothetically [123,124].

There is evidence of neurological complications with SARS and MERS, and a growing body of evidence for neurological complications with COVID-19. The etiology of these neurological symptoms is less clear; they may be directly caused by the viral infection or they could be due to other conditions, such as sepsis, coagulation disorders, cytokine release, and vasculitis, all of which have been reported in COVID-19 patients. Much more needs to be learned, but clinicians must be aware and prepared for the possibility and potentiality of COVID-19 neurological symptoms.

The evidence that the SARS-CoV-2 can enter the CNS is alarming. While autopsy studies show definitive proof that the earlier SARS-CoV was found in brain tissue, viral levels were lower in the brain than in the lungs [125]. The route by which the SARS-CoV-2 virus enters the CNS and its effects on the CNS remain to be elucidated.

It is important to learn more about chronic neurological complications related to COVID-19. The blood-brain barrier, which may protect patients from invading pathogens, is a two-way street and could in theory at least prevent viruses from being expelled from the brain [50]. Further study is needed, particularly as the population of COVID-recovered patients grows and may have to manage long-term consequences of the infection.

Limitations

COVID-19 is a complex condition that has yet to be fully elucidated. New information appears daily in the medical literature and some earlier concepts about the disease have been revised. This article was produced during the pandemic and may reflect an incomplete understanding of the neurological consequences of COVID-19.

Conclusion

Neurological impairment has been reported with the coronaviruses related to the earlier SARS and MERS epidemics, and there is growing awareness of what may be potentially serious neurological effects of the virus associated with COVID-19. While most COVID-19 patients develop respiratory symptoms prior to or to the exclusion of neurological symptoms, atypical COVID-19 cases have occurred. Neurological symptoms may be mild, such as headache, dizziness, or altered consciousness or may include encephalitis, which might also be the result of critical illness. The link between neurological involvement and respiratory failure has been suspected but remains to be investigated. Clinicians should be aware of neurological symptoms in their patients.

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ORCID

Joseph V. Pergolizzi Jr  <http://orcid.org/0000-0001-5658-1471>
 Robert B. Raffa  <http://orcid.org/0000-0002-1456-4451>
 Giustino Varrassi  <http://orcid.org/0000-0002-3822-2923>
 Peter Magnusson  <http://orcid.org/0000-0001-7906-7782>
 Jo Ann LeQuang  <http://orcid.org/0000-0003-4794-0318>
 Antonella Paladini  <http://orcid.org/0000-0002-1219-9315>
 Robert Taylor  <http://orcid.org/0000-0001-5971-361X>

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